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Cold Spells and Cause-Specific Mortality in 47 Japanese Prefectures: A Systematic Evaluation

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Background: Many studies have investigated the devastating health effects of heat waves, but less is known about health risks related to cold spells, despite evidence that extreme cold may contribute to a larger proportion of deaths.

Objectives: We aimed to systematically investigate the association between cold spells and mortality in Japan.

Methods: Daily data for weather conditions and 12 common causes of death during the 1972–2015 cold seasons (November–March) were obtained from 47 Japanese prefectures. Cold spells were defined as ≥ 2 consecutive days with daily mean temperatures ≤ 5th percentile for the cold season in each prefecture. Quasi-Poisson regression was combined with a distributed lag model to estimate prefecture-specific associations, and pooled associations at the national level were obtained through random-effects meta-analysis. The potential influence of cold spell characteristics (intensity, duration, and timing in season) on associations between cold spells and mortality was examined using a similar two-stage approach. Temporal trends were investigated using a meta-regression model.

Results: A total of 18,139,498 deaths were recorded during study period. Mortality was significantly higher during cold spell days vs. other days for all selected causes of death. Mortality due to age-related physical debilitation was more strongly associated with cold spells than with other causes of death. Associations between cold spells and mortality from all causes and several more specific outcomes were stronger for longer and more intense cold spells and for cold spells earlier in the cold season. However, although all outcomes were positively associated with cold spell duration, findings for cold spell intensity and seasonal timing were heterogeneous across the outcomes. Associations between cold spells and mortality due to cerebrovascular disease, cerebral infarction, and age-related physical debility decreased in magnitude over time, whereas temporal trends were relatively flat for all-cause mortality and other outcomes.

Discussion: Our findings may have implications for establishing tailored public health strategies to prevent avoidable cold spell–related health consequences. https://doi.org/10.1289/EHP7109

Introduction

Over the past two decades, multiple epidemiological studies have reported on heat-related health risks (Anderson and Bell 2009; Basu 2009; Gasparrini et al. 2015a; Guo et al. 2017, 2018; Kovats and Hajat 2008; Zhao et al. 2019). In contrast, fewer studies have analyzed cold effects, despite evidence showing that cold weather contributes to more deaths than hot weather (Chen et al. 2018; Fu et al. 2018; Gasparrini et al. 2015b; Guo et al. 2014; Pascal et al. 2018; Petkova et al. 2021). For example, a global study reported that 10.12% of nonaccidental mortality was attributable to nonoptimum temperatures, with estimated attributable fractions for Japan of 9.81% for cold and only 0.32% for heat (Gasparrini et al. 2015b).

A cold spell, which is a discrete period during the cold season characterized by a sudden significant drop in temperature (Ebi and Mills 2013), may be more life-threatening than a single-day cold event due to extra strain on the body's thermoregulatory system (Chen et al. 2017). Moreover, the health impacts of cold may persist for more than 2 wk, which makes it difficult to evaluate a dose–response relationship and infer causality (Ryti et al. 2016).

To date, few studies have considered whether mortality related to cold spells varies by cause of death, which may be helpful in identifying population subgroups who are especially vulnerable to cold-related effects. Population susceptibility to cold spells may also change over time due to improvements in social, environmental, behavioral, health care, and well-being factors (Arbuthnott et al. 2016; Ebi and Mills 2013), but few studies have examined temporal trends in cold spell–related mortality over the past decades (Chung et al. 2017; Vicedo-Cabrera et al. 2018). Furthermore, relatively few studies have examined whether associations between cold spells and mortality are influenced by the intensity, duration, or seasonal timing of cold spells (Barnett et al. 2012; Kysely et al. 2009).

Cold spells are expected to become more common with climate change (Barnett et al. 2012; Karl et al. 2008), and Japan's rapidly aging population may be especially vulnerable to extreme cold (Anderson and Bell 2009; Chen et al. 2019). Therefore, increasing our understanding of the health effects of cold spells will be important to address the complex, long-term public health challenges caused by climate change. For the present study, we used a national data set covering 47 Japanese prefectures during 1972–2015 to investigate: *a*) the impact of cold spells on all-cause and cause-specific mortality, *b*) temporal variation in cold spell–mortality associations, and *c*) associations between cold spell characteristics and cold spell mortality effects.

Methods

Data Collection

Japan is located in the Pacific Ocean off the East Asian coast and is divided into 47 prefectures. Prefectural areas range from 83,424 km^2 (Hokkaido) to 1,876 km^2 (Kagawa) (Geospatial

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Information Authority of Japan). The prefectures of Tokyo and Tottori have the largest and smallest populations (13,515,000 and 573,000 in 2015, respectively) (Ministry of Internal Affairs and Communication 2019). Daily mortality data were collected from the Ministry of Health, Labor and Welfare of Japan for deaths in Okinawa during the period 1973–2015, and deaths during the period 1972–2015 in all other prefectures. The causes of death were categorized using the International Classification of Diseases, 8th Revision (ICD-8) for deaths in the period 1972–1978, ICD-9 for deaths in the period 1979–1994, and ICD-10 for deaths during and after 1995. Thirteen underlying causes of death were extracted: circulatory disease (ICD-8: 390–458, ICD-9: 390–459; and ICD-10: I00–I99), ischemic heart disease (IHD) (ICD-8: 410–414; ICD-9: 410–414; and ICD-10: I20–I25), cerebrovascular disease (ICD-8: 430–438; ICD-9: 430–438; and ICD-10: I60–I69), cerebral hemorrhage (ICD-8: 430–431; ICD-9: 430–432; and ICD-10: I60–I62), cerebral infarction (ICD-8: 432–435 or 437; ICD-9: 433–435 or 437; and ICD-10: I65–I66 or I63), age-related physical debilitation (ICD-8: 794; ICD-9: 797; and ICD-10: R54), respiratory disease (ICD-8: 460–519; ICD-9: 460–519; and ICD-10: J00–J99), pneumonia (ICD-8: 480–486; ICD-9: 480–486; and ICD-10: J12–J18), flu (ICD-8: 470–474; ICD-9: 487; and ICD-10: J10–J11), asthma (ICD-8: 493; ICD-9: 493; and ICD-10: J45–J46), chronic obstructive pulmonary disease (COPD) (ICD-8: 491–492; ICD-9: 491–492 or 496; and ICD-10: J41–J44), emphysema (ICD-8: 492; ICD-9: 492; and ICD-10: J43), and renal disease (ICD-8: 580–599; ICD-9: 580–599; and ICD-10: N00–N39). These outcomes were selected because they are among the most common causes of death in Japan (Ma et al. 2019).

Hourly weather data, including temperature (degrees Celsius) and relative humidity (RH) (%), were obtained for the study period from the Japan Meteorological Agency. Daily maximum and minimum temperatures were calculated as the highest and lowest hourly measurements on each day, with daily mean temperature and mean RH as the 24-h averages. For each prefecture, a single weather station located in the most highly populated area of the capital city was selected.

Definition of a Cold Spell

In the present study, we defined cold spells as ≥ 2 consecutive days with daily mean temperatures lower than the prefecture-specific 5th percentile cold season daily mean temperature for the period 1972–2015, consistent with the "optimum" definition (based on model fit) identified in a recent study of cold spells and mortality in China (Chen et al. 2019).

Statistical Analyses

Our data analyses were restricted to the cold season (from November to March).

A two-stage analytic strategy was applied to evaluate the association between cold spells and mortality (Chen et al. 2019; Gasparrini et al. 2012, 2015b). First, we estimated prefecture-specific mortality risks for mortality on cold spell days compared with other days, then we derived pooled estimates at the national level using a meta-analysis.

First stage. For each prefecture, the mortality risk of mortality on cold spell days compared with non–cold spell days was estimated using a quasi-Poisson regression combined with a distributed lag model (DLM) (Xie et al. 2013). An algebraic expression of the model is given by:

$$\begin{aligned} log\,(\mu_t) &= \alpha + \beta T_{t,l}(CS_t) + NS(Dos_t, df = 4) + \eta Season_t + \gamma DOW_t \\ &\quad + \nu Holiday_t + NS(RH_t, df = 3) + \lambda Flu_t \\ &= \alpha + \beta T_{t,l}(CS_t) + COVs \end{aligned} \tag{1}$$

where μ_t is the estimated number of deaths on day t; CS_t is a binary variable for a cold spell day; $T_{t,l}$ (.) is the cross-basis function combining the exposure–response function and a natural cubic spline (NS) with 3 degrees of freedom (df) for the lag–response function, with l a maximum lag of 21 d to account for delayed cold effects (Gasparrini et al. 2015b; Yang et al. 2015); $NS(Dos_t, df = 4)$ is an NS with 4 df for day of the season (1, 2, 3, …, 151 or 152) to capture seasonality; $Season_t$ is a categorical variable for each season (1 for November 1972–March 1973, 2 for November 1973–March 1974, and so on) to control for long-term trend; DOW_t is a categorical variable representing day of the week; $Holiday_t$ is a binary variable indicating public holidays; $NS(Hum_t, df = 3)$ is an NS with 3 df to control for daily mean RH; Flu_t is a binary variable with 1 indicating a day with occurrence of influenza deaths and 0 otherwise; $COVs$ stands for all other covariates in the model.

Cold spell characteristics. To estimate the influence of cold spell intensity, duration, and seasonal timing, we modeled the relationship between cold spell characteristics and mortality on cold-spell days (Chen et al. 2020). Equation (1) was modified as follows:

$$\begin{aligned} log\,(\mu_t) &= \alpha + \beta_1 CI_t + \beta_2 CD_t + \beta_3 CT_t + \eta Season_t + \gamma DOW_t \\ &\quad + \nu Holiday_t + NS(RH_t, df = 3) + \lambda Flu_t \end{aligned} \tag{2}$$

where CI_t is cold spell intensity on day t, defined as the difference between the temperature on day t and the prefecture-specific threshold, which is zero for temperatures at or above the threshold. CD_t is a continuous variable indicating the duration of the cold spell as of day t, which is zero on the first day, one on the second day, etc. CT_t is a continuous variable representing the seasonal timing of the cold spell, defined as the difference in days between day t and the first day of the cold season (1 November) (Barnett et al. 2012).

Second stage. In the second stage, prefecture-specific mortality risks were pooled using random-effect meta-analyses with restricted likelihood estimation (Gasparrini and Armstrong 2011).

Temporal variation in cold spell–mortality associations. A similar two-stage time-series design was applied to explore temporal changes in associations between cold spells and mortality during the study period. First, prefecture season-specific effects were estimated using Equation (1). Then in the second stage, a random-effects meta-regression model was applied to evaluate long-term variation in cold spell-associated mortality at the national level, with season (linear) and prefecture season-specific coefficients modeled as independent and dependent variables, respectively (Ma et al. 2019; Zapata-Diomedi et al. 2019; Zhao et al. 2019). The meta-regression model can be described as follows:

$$\widehat{\beta}_{i,j} = \theta_0 + \theta_i x_{i,j} + \nu_i + \varepsilon_{i,j} \tag{3}$$

where $\widehat{\beta}_{i,j}$ is the estimated prefecture season-specific estimate for season i in prefecture j; θ_0 is the average partial coefficient over the whole study period; θ_i is the average change in the partial coefficient for a unit increase in the effect of cold spell for the season variable $x_{i,j}$ (1 for November 1972–March 1973, 2 for November 1973–March 1974, and so on); ν_i and $\varepsilon_{i,j}$ are the random effect of the prefecture-specific deviation and random error, respectively (Chen et al. 2020; Yang et al. 2019).

Sensitivity analyses. A series of sensitivity analyses were conducted. We used different temperature indices (mean, minimum, and maximum daily temperatures) durations (2, 3, or 4 d), and intensities (temperature thresholds at the 2.5th, 5th, or 7.5th percentile for the cold season in each prefix) to generate 26 additional cold spell definitions (Table S1). We also evaluated alternative df for the NS of lag days (3–6), RH (3–6), and day of the season (4–7). In addition, we added an NS of time to the first-stage model with 1–3 df per decade to control for long-term trends (Gasparrini et al. 2015a). Furthermore, we replaced $Season_t$ and Dos_t in Equation (1) with an NS of time (1, 2, 3, . . ., 6,503) with 3–4 df per season to adjust for the long-term trend and seasonality. Finally, instead of using a linear term for the season variable, we fitted a random-effects meta-regression model that included a restricted cubic spline function with 3 knots on the season term to test the assumption of a linear temporal trend (Perperoglou et al. 2019).

R software (version 3.6.1; R Foundation for Statistical Computing) was used to perform all statistical analyses. The "dlnm" package was used to examine the prefecture-specific relationship between cold spells and mortality (Gasparrini et al. 2010), and the "metafor" package was used to fit the meta-analysis (Viechtbauer 2010). Two-tailed p-values less than 0.05 were considered statistically significant for all statistical tests.

Results

Average daily mean temperatures during cold seasons across the study period (1972–2015) were highest in Okinawa (18.6 ± 3.1°C) and lowest in Hokkaido (–0.5 ± 4.5°C) (Table 1; Figure S1). There were 18,139,498 deaths from all causes, including 6,522,294 (35.96%) from circulatory diseases; 2,391,071 (13.18%) from respiratory diseases; 412,984 (2.28%) from renal disease; and 681,619 (3.76%) from age-related physical debility (Tables S2–S3). The average number of cold spells per season during the study period ranged from 1.5 to 2.1, and the average number of cold spell days was 5–6 (Table S4).

Cold spells were associated with an immediate increase in mortality for all outcomes except COPD and emphysema, where associations were evident after 1–2 d (Figure 1). Associations remained positive for all outcomes for ≥15 d, with associations lasting at least 21 d for overall respiratory disease and pneumonia.

For all outcomes, estimated effects of cold spells were substantially higher for a cumulative lag of 0–14 d compared with

Table 1. Descriptive statistics for average number of daily all-cause mortality and weather conditions in 47 Japanese prefectures during 1972–2015 cold seasons.

Prefecture	All-cause	Minimum temperature (°C)	Mean temperature (°C)	Maximum temperature (°C)	Relative humidity (%)
Hokkaido	118 ± 31	–4.0 ± 4.5	–0.5 ± 4.5	2.7 ± 4.9	68.4 ± 9.6
Aomori	36 ± 10	–1.7 ± 3.8	1.6 ± 4.2	5.0 ± 5.1	74.8 ± 9.3
Iwate	37 ± 70	–2.9 ± 4.2	1.1 ± 4.1	5.3 ± 4.7	72.2 ± 10.9
Miyagi	50 ± 129	0.7 ± 3.7	4.4 ± 4.0	8.4 ± 4.6	65.1 ± 10.7
Akita	33 ± 9	–0.3 ± 3.7	2.9 ± 4.0	6.2 ± 4.8	71.7 ± 10.0
Yamagata	34 ± 8	–1.1 ± 3.7	2.5 ± 4.0	6.6 ± 5.0	77.4 ± 10.1
Fukushima	54 ± 25	0.5 ± 3.7	4.4 ± 3.9	8.9 ± 4.9	66.2 ± 10.8
Ibaraki	66 ± 17	0.6 ± 4.3	5.8 ± 3.8	11.5 ± 4.2	67.8 ± 13.3
Tochigi	46 ± 12	0.1 ± 4.5	5.4 ± 4.0	11.2 ± 4.3	63.4 ± 12.6
Gunma	47 ± 12	1.8 ± 3.9	6.2 ± 3.8	11.6 ± 4.4	56.1 ± 12.3
Saitama	111 ± 41	2.0 ± 4.0	6.7 ± 3.7	12.2 ± 4.3	57.6 ± 14.3
Chiba	103 ± 35	4.4 ± 3.9	8.3 ± 3.8	12.4 ± 4.2	59.5 ± 15.8
Tokyo	229 ± 60	5.0 ± 3.7	8.6 ± 3.7	12.5 ± 4.1	53.2 ± 15.2
Kanagawa	136 ± 48	4.8 ± 3.8	8.4 ± 3.7	12.4 ± 4.1	57.8 ± 15.2
Niigata	63 ± 14	2.3 ± 3.6	5.4 ± 3.9	8.7 ± 4.7	71.4 ± 9.6
Toyama	28 ± 7	2.1 ± 3.8	5.6 ± 4.3	9.6 ± 5.3	78.5 ± 10.8
Ishikawa	27 ± 7	3.0 ± 3.7	6.4 ± 4.2	10.1 ± 5.0	72.2 ± 10.3
Fukui	20 ± 6	2.4 ± 3.7	6.0 ± 4.1	10.1 ± 5.1	77.9 ± 9.2
Yamanashi	22 ± 6	0.7 ± 4.5	6.0 ± 4.0	12.1 ± 4.5	59.3 ± 15.7
Nagano	56 ± 12	–1.5 ± 4.1	2.5 ± 4.3	7.4 ± 5.3	74.8 ± 9.1
Gifu	48 ± 12	3.0 ± 4.0	7.3 ± 4.0	12.2 ± 4.5	65.1 ± 12.2
Shizuoka	81 ± 22	4.6 ± 4.3	9.4 ± 3.7	14.1 ± 4.0	60.1 ± 14.7
Aichi	128 ± 35	3.3 ± 4.0	7.4 ± 3.9	12.1 ± 4.4	63.3 ± 12.0
Mie	45 ± 11	4.1 ± 3.9	7.8 ± 3.8	12.0 ± 4.0	63.6 ± 11.4
Shiga	27 ± 8	3.0 ± 3.8	6.4 ± 3.8	10.0 ± 4.3	74 ± 10.0
Kyoto	58 ± 13	3.4 ± 3.9	7.4 ± 3.9	12.1 ± 4.4	66.4 ± 9.3
Osaka	171 ± 43	5.1 ± 3.8	8.6 ± 3.9	12.5 ± 4.3	61.1 ± 10.5
Hyogo	121 ± 67	4.9 ± 4.1	8.3 ± 4.1	12.0 ± 4.2	62.3 ± 9.9
Nara	29 ± 9	2.0 ± 3.9	6.5 ± 3.8	11.8 ± 4.4	71.3 ± 10.9
Wakayama	30 ± 7	4.9 ± 3.8	8.7 ± 3.9	12.7 ± 4.4	62.7 ± 10.6
Tottori	17 ± 5	2.9 ± 3.7	6.8 ± 4.1	11.1 ± 5.0	73.8 ± 9.9
Shimane	23 ± 6	3.2 ± 3.7	6.9 ± 3.8	11.2 ± 4.7	74.8 ± 10.2
Okayama	49 ± 11	3.1 ± 4.1	7.4 ± 3.9	12.1 ± 4.1	66.6 ± 10.5
Hiroshima	66 ± 15	3.9 ± 3.9	7.8 ± 3.9	12.4 ± 4.2	67.5 ± 10.2
Yamaguchi	43 ± 10	2.5 ± 4.1	7.1 ± 4.0	12.4 ± 4.6	73.7 ± 10.0
Tokushima	23 ± 6	5.0 ± 3.9	8.7 ± 3.9	12.7 ± 4.2	61.8 ± 11.4
Kagawa	27 ± 7	3.8 ± 4.0	8.1 ± 3.8	12.3 ± 4.1	65.1 ± 12.0
Ehime	41 ± 10	4.6 ± 3.9	8.6 ± 3.9	12.8 ± 4.3	63.8 ± 11.4
Kochi	25 ± 6	4.5 ± 4.5	9.3 ± 4.1	14.8 ± 4.1	62.5 ± 12.8
Fukuoka	109 ± 25	5.8 ± 3.8	9.3 ± 3.9	13.1 ± 4.5	64.2 ± 11.4
Saga	23 ± 6	4.3 ± 4.2	8.5 ± 4.0	13.2 ± 4.5	69.0 ± 10.4
Nagasaki	40 ± 9	6.3 ± 4.0	9.7 ± 4.0	13.5 ± 4.5	66.4 ± 10.8
Kumamoto	48 ± 11	3.9 ± 4.6	8.7 ± 4.3	13.8 ± 4.7	69.6 ± 10.6
Oita	33 ± 8	4.6 ± 4.2	8.8 ± 3.8	13.2 ± 4.2	65.2 ± 12.7
Miyazaki	30 ± 8	5.5 ± 4.6	10.3 ± 4.0	15.5 ± 4.1	68.9 ± 13.3
Kagoshima	52 ± 11	6.8 ± 4.7	11.1 ± 4.2	15.8 ± 4.3	67.6 ± 11.1
Okinawa	21 ± 7	16.3 ± 3.2	18.6 ± 3.1	21.2 ± 3.3	69.4 ± 11.5

Note: SD, standard deviation.

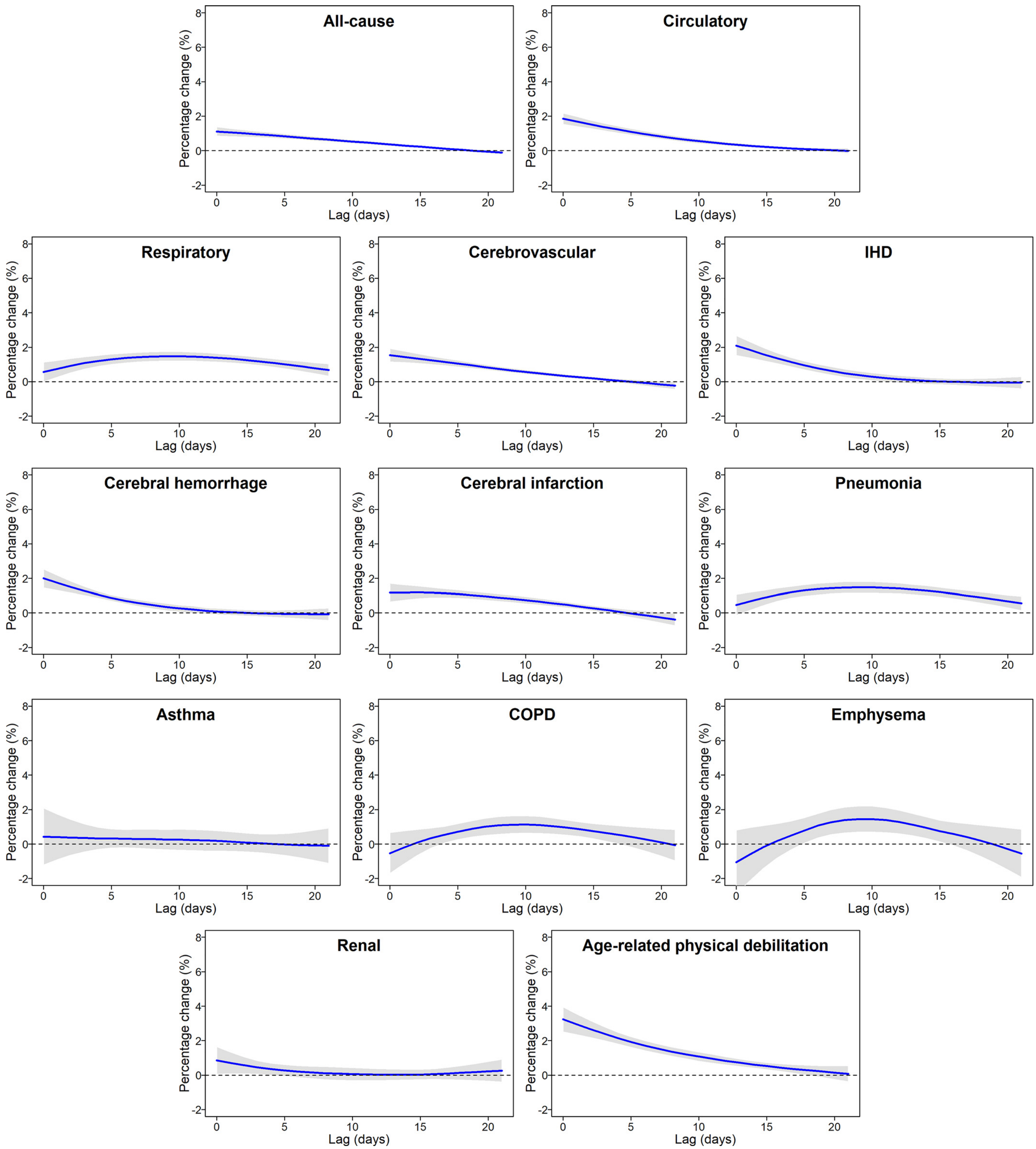

Figure 1. Overall lag structure (0–21 d) in effects of cold spell on cause-specific mortality in 47 Japanese prefectures during the period 1972–2015. Cold spells were defined as ≥2 consecutive days with daily mean temperatures lower than the prefecture-specific 5th percentile cold season daily mean temperature (for 1972–2015). Prefecture-specific cold spell–mortality associations were estimated using quasi-Poisson regression with a distributed lag model, which were then pooled using random-effect meta-analyses with restricted likelihood estimation. Gray bands are 95% confidence intervals.

lag 0 (Table 2). In most cases associations were slightly stronger for a cumulative lag of 0–21 d, with more substantial increases for overall respiratory mortality and pneumonia. The association between cold spells and mortality was strongest for age-related physical debility, which was 31% higher (95% CI: 25%, 37%; lag 0–21 d) on cold spell days compared with other days. The between-prefecture heterogeneity of associations between cold spells and mortality (lag 0–21) varied greatly by cause, with mean I^2 of 44.96% (range: 0.01%–85.93%) (Figure 2; Figures S2–S13).

Table 2. Estimated percentage increase in mortality on cold spell days compared with non–cold spell days during the 1972–2015 cold seasons (November–March) based on pooled estimates for 47 Japanese prefectures over lag 0, lag 0–14 and lag 0–21 d.

Causes of death	Lag 0 (95% CI)	Lag 0–14 (95% CI)	Lag 0–21 (95% CI)
All-cause	1.11 (0.85, 1.38)	11.00 (8.92, 13.12)	11.30 (8.93, 13.73)
Circulatory	1.86 (1.54, 2.18)	15.05 (12.46, 17.70)	15.68 (12.94, 18.48)
Respiratory	0.58 (0.03, 1.13)	19.65 (15.14, 24.33)	28.05 (21.72, 34.71)
Cerebrovascular	1.54 (1.16, 1.93)	14.00 (11.43, 16.63)	13.51 (10.77, 16.31)
IHD	2.10 (1.53, 2.67)	12.77 (9.35, 16.31)	12.74 (8.55, 17.09)
Cerebral hemorrhage	2.00 (1.47, 2.54)	11.28 (8.92, 13.70)	10.67 (7.84, 13.57)
Cerebral infarction	1.18 (0.65, 1.71)	14.20 (10.99, 17.50)	12.76 (9.57, 16.04)
Pneumonia	0.48 (–0.12, 1.07)	19.92 (14.79, 25.26)	27.59 (20.43, 35.17)
Asthma	0.41 (–1.23, 2.08)	3.06 (–3.84, 10.44)	2.07 (–6.32, 11.23)
COPD	–0.52 (–1.68, 0.66)	9.64 (3.79, 15.83)	11.62 (3.22, 20.72)
Emphysema	–1.04 (–2.87, 0.82)	9.51 (–0.54, 20.58)	9.85 (–3.28, 24.76)
Renal	0.86 (0.06, 1.66)	3.63 (–0.52, 7.96)	4.19 (–1.26, 9.94)
Age-related physical debilitation	3.24 (2.52, 3.96)	28.25 (23.41, 33.29)	30.69 (24.87, 36.77)

Note: Cold spells were defined as ≥2 consecutive days with daily mean temperatures lower than the prefecture-specific 5th percentile cold season daily mean temperature (for 1972–2015). Prefecture-specific cold spell–mortality associations were estimated using quasi-Poisson regression with a distributed lag model, which were then pooled at the national level using random-effect meta-analyses with restricted likelihood estimation. Seasonality, long-term trend, day of the week, holidays, occurrence of influenza, and daily mean relative humidity were controlled for. CI, confidence interval; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease.

All-cause mortality was slightly higher for more intense cold spells (0.38%; 95% CI: 0.02, 0.73% for a 1°C decrease in daily mean temperature relative to the prefecture-specific 5th percentile), and longer cold spells (0.92%; 95% CI: 0.69,1.16% for a 1-d increase in duration), but slightly lower for cold spell days later in the season (–0.53%; 95% CI: –0.77, 0.29% for a 10-d increase in cold-season day) (Table 3; Table S5). Longer cold spells were positively associated with mortality for all cause-specific outcomes, though many effect estimates were close to the null and/or not significant for the less common causes of death. Associations with cold spell intensity were more heterogeneous, though all significant associations were positive. In contrast, although for most outcomes associations were stronger for earlier cold spells, respiratory mortality and pneumonia deaths were significantly higher for cold spells later in the season. The pattern of associations across the three cold spell characteristics were significant and consistent with the pattern for all-cause mortality (higher mortality for more intense and longer cold spells, lower mortality for cold spells later in the season), for deaths attributed to circulatory diseases, IHD, and age-related physical debility mortality.

Temporal trends in associations between cold spells and mortality (lag 0–21) over the study period (1972–2015) were negative (indicating weaker associations over time) for most outcomes, though none of the positive associations (for respiratory diseases, pneumonia, emphysema, and renal diseases) were significant (Figure 3). Significant decreases over time were limited to mortality due to cerebrovascular disease (slope estimate = –0.0032; $p = 0.037$) and cerebral infarction (slope estimate = –0.0066; $p = 0.017$), though the negative trend for age-related physical debility approached significance (slope estimate = –0.0054; $p = 0.06$).

We recalculated mortality risks during cold spell periods compared with non–cold spell periods based on different cold-spell definitions. In general, effect estimates did not change much when using different definitions, with larger effect estimates for overall respiratory mortality and pneumonia mortality when using daily minimum temperature as the temperature metric (Figure S14; Tables S6–S7). For example, the effect estimates (95% CI) for respiratory mortality and pneumonia mortality were 40.10% (32.93%, 47.67%) and 36.94% (29.63%,44.66%), respectively, when we defined cold spells as ≥2 consecutive days with daily minimum temperatures lower than the prefecture-specific 5th percentile cold season daily minimum temperature, compared with 29.39% (22.66%, 36.49%) and 28.14% (20.82%, 35.90%) when using the daily mean temperature as the temperature indicator. There was little change in the association between all-cause mortality and cold spells for a cumulative lag of 0–21 d when alternative df were used to model natural splines of RH, day of the season, and the cold spell lag (Table S8), and when we relaxed the assumption of a linear temporal trend over the study period (Figure S15). Effect estimates increased slightly when we additionally adjusted for long-term time trends using a natural spline with 1–3 df per decade (12.70–13.93% compared with 11.57% for the primary model estimate), and were attenuated when the categorical variable for each annual season and the natural spline of day of the season were removed from the model and replaced with a natural spline of time with 3 or 4 df/y (7.63%; 95% CI: 4.90, 10.44% and 8.63%; 95% CI: 6.43, 10.88%, respectively).

Discussion

To our knowledge, this is the first nationwide study to comprehensively characterize the association between cold spells and mortality in Japan according to cause-specific outcomes, temporal variation, and cold spell characteristics. We found that cold spells were significantly associated with increased mortality risks from a spectrum of diseases, with the strongest association estimated for mortality due to age-related physical debility. Our results suggested immediate increases in mortality for most outcomes, and associations that persisted for more than 15 d for all outcomes. Associations between all-cause mortality and cold spells were stronger for cold spells that were more intense, longer, and that occurred earlier during the cold season. Several of the more specific outcomes followed a similar pattern, including mortality attributed to circulatory diseases, IHD, and age-related physical debility. However, associations with several other outcomes showed no relation or nonsignificant inverse relations with cold-spell intensity, and associations between cold spells and mortality due to respiratory diseases and pneumonia were significantly stronger for cold spells that occurred later in the cold season. Over the 44-y study period, there was no significant temporal change in cold spell–related deaths from all causes and most selected diseases at the national level, whereas we observed significant declining trends in mortality risks from cold spells for cerebrovascular disease and cerebral infarction, and a borderline-significant declining trend in mortality risk from age-related physical debility.

Despite using various cold spell definitions, lags, and reference periods, our observation that cold spells could have detrimental impact on human health is consistent with findings from other countries. A study of cold spells and mortality in Moscow during 2000–2006 reported significantly higher all-cause, IHD,

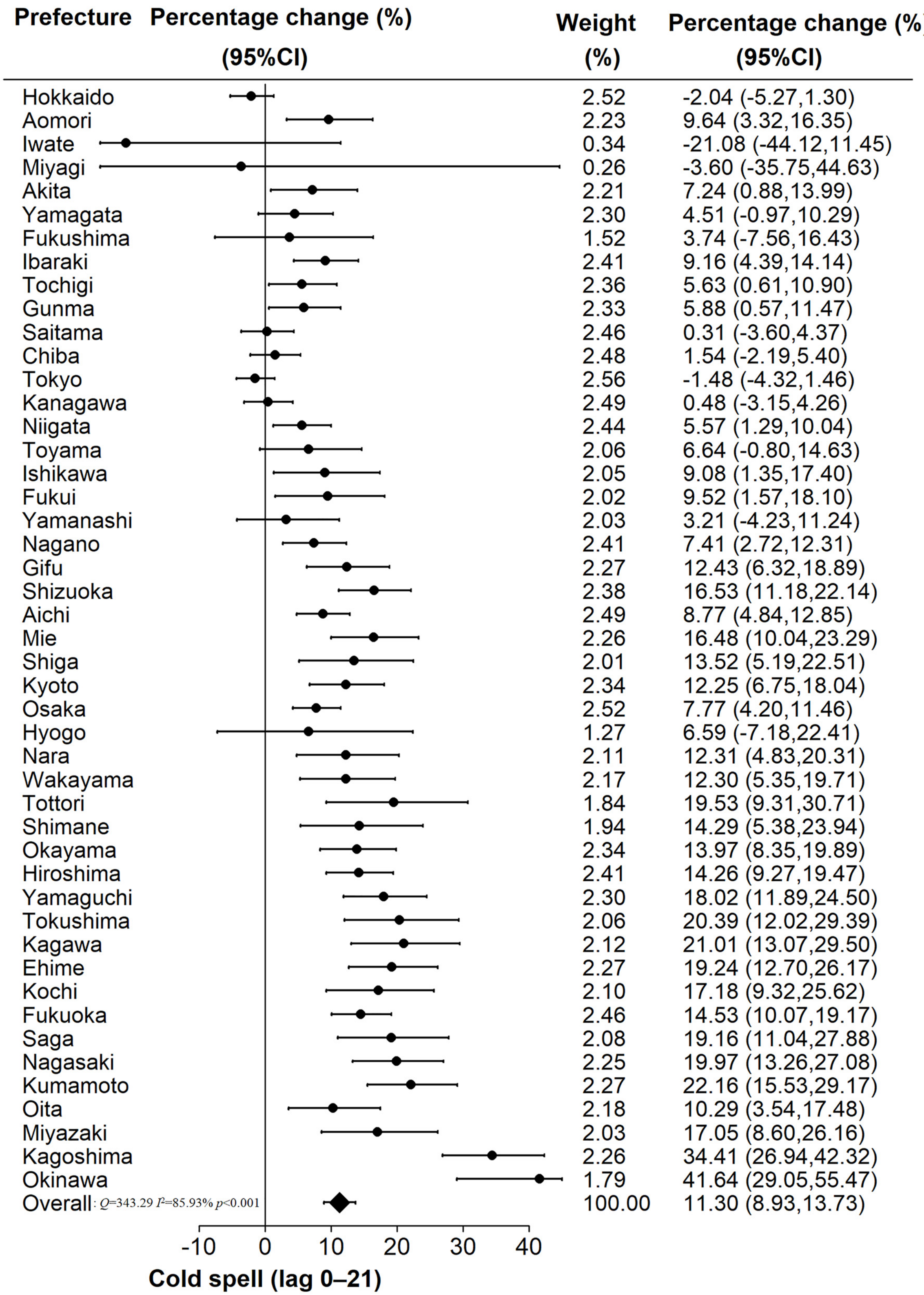

Figure 2. Estimated percentage increase in all-cause mortality on cold spell days compared with non–cold spell days during the 1972–2015 cold seasons (November–March) in 47 Japanese prefectures over lag 0–21 d. Cold spells were defined as ≥2 consecutive days with daily mean temperatures lower than the prefecture-specific 5th percentile cold season daily mean temperature (for 1972–2015). Prefecture-specific cold spell–mortality associations were estimated using quasi-Poisson regression with a distributed lag model, which were then pooled using random-effect meta-analyses with restricted likelihood estimation. Note: CI, confidence interval.

Table 3. The pooled percentage increase in mortality risk during a cold spell per unit increase in cold spell characteristic over lag 0–21 d in Japan during the period 1972–2015.

Causes of death	Intensity, 1°C increase[a] (95% CI)	Seasonal timing, 10-d increase[b] (95% CI)	Duration, 1-d increase[c] (95% CI)
All-cause	0.38 (0.02, 0.73)	–0.53 (–0.77, –0.29)	0.92 (0.69, 1.16)
Circulatory	0.81 (0.33, 1.29)	–0.77 (–1.05, –0.49)	1.12 (0.83, 1.41)
Respiratory	0.62 (–0.39, 1.62)	1.17 (0.38, 1.96)	0.55 (–0.10, 1.20)
Cerebrovascular	–0.03 (–0.77, 0.71)	–0.48 (–0.88, –0.07)	1.06 (0.67, 1.45)
IHD	1.63 (0.50, 2.74)	–1.56 (–2.23, –0.88)	0.96 (0.26, 1.66)
Cerebral hemorrhage	1.36 (0.17, 2.53)	–0.31 (–1.15, 0.53)	0.61 (0.02, 1.20)
Cerebral infarction	–0.96 (–2.07, 0.14)	–0.54 (–1.17, 0.10)	1.28 (0.54, 2.03)
Pneumonia	0.80 (–0.46, 2.04)	1.11 (0.16, 2.08)	0.68 (–0.18, 1.56)
Asthma	–0.83 (–4.66, 2.85)	–0.38 (–2.39, 1.66)	0.84 (–1.13, 2.86)
COPD	0.97 (–3.03, 4.81)	–0.30 (–2.16, 1.61)	0.36 (–1.4, 2.16)
Emphysema	0.65 (–4.29, 5.35)	–0.82 (–3.66, 2.10)	0.19 (–2.55, 3.02)
Renal	–0.06 (–2.37, 2.20)	–1.54 (–2.93, –0.14)	1.00 (–0.29, 2.31)
Age-related physical debilitation	1.66 (0.23, 3.06)	–1.60 (–2.64, –0.54)	2.24 (1.48, 3.00)

Note: Cold spells were defined as ≥ 2 consecutive days with daily mean temperatures lower than the prefecture-specific 5th percentile cold season daily mean temperature (for the period 1972–2015). Prefecture-specific associations between cold spell characteristics and cold spell mortality effects were estimated using quasi-Poisson regression with a distributed lag model, with the cold spell characteristic as an independent variable, which were then pooled at the national level using random-effect meta-analyses with restricted likelihood estimation. Seasonality, long-term trend, day of the week, holidays, occurrence of influenza, and daily mean relative humidity were controlled for. COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; SD, standard deviation.

[a]1°C increase in intensity, defined according to the daily mean temperature distribution in each prefecture as follows: If temperature on day t is $\geq$5th percentile, intensity = 0, otherwise intensity = temperature at the 5th percentile temperature on day t.

[b]10-d increase in timing during cold season (November–March), where timing is a continuous variable indicating the number of days between November 1 and day t.

[c]1-d increase in the duration of the cold spell, modeled as a continuous variable with the first day = 0.

and CVD mortality among elderly residents (age ≥ 74 y) on days during cold spells compared with the same calendar days in the absence of cold spells (Revich and Shaposhnikov 2008). The authors identified only two cold spells during the study period (defined as ≥ 9 consecutive days with daily mean temperatures below the 3rd percentile for the same month, including ≥ 6 d with daily mean temperatures below the 1st percentile), which were separated by only 6 non–cold spell days. A study of four cold spells and mortality in Netherlands during 1979–1997 reported significantly higher all-cause and cardiovascular mortality (all ages combined) on days during the first 3 cold spells compared with 31-d moving average mortality rates for the same days during the 2 y before each cold spell (Huynen et al. 2001). During the two most recent cold spells, mortality was significantly higher among those age ≥ 65 y. For this analysis, cold spells were defined as ≥ 9 d with minimum temperatures ≤ -5°C, including at least 6 d with minimum temperatures ≤ -10°C. A study of cold spells and mortality in 31 Chinese cities during the period 2007–2013 used a two-stage approach similar to our analysis (Chen et al. 2019). The authors reported a pooled cumulative relative risk (lag 0–27) of 1.55 (95% CI: 1.40, 1.70) for nonaccidental mortality on cold spell days compared with non–cold spell days, with cold spells defined as ≥ 2 consecutive days with daily mean temperatures below the 5th percentile for each city. A systematic review and meta-analysis showed that cold spells were associated with a pooled relative risk of 1.10 (95% CI: 1.04, 1.17) for all-cause or nonaccidental mortality, 1.11 (95% CI: 1.03, 1.19) for mortality from cardiovascular diseases, and 1.21 (95% CI: 0.97, 1.51) for mortality from respiratory diseases based on estimates in several Asian and European cities (Ryti et al. 2016).

Various underlying mechanisms have been postulated to account for higher mortality during cold spells. Exposure to cold could lead to circulatory stress by causing an increase in plasma cholesterol, plasma fibrinogen, blood viscosity, arterial pressure, and platelet and red cell counts (Keatinge et al. 1984). Rapid deaths could occur due to the rupture of atheromatous plaques during hypertension and cold-triggered coronary spasm (The Eurowinter Group 1997). Breathing cold air can elicit a vasoconstrictive reflex in the nose and upper airways that may suppress immune responses to respiratory infections and thus increase the risk of respiratory disease mortality (Mäkinen et al. 2009). As for the cold spell–aggravated renal mortality, we hypothesize that prolonged exposure to cold weather could result in blood clots in the veins and arteries in and around the kidneys, as well as cholesterol deposits that block blood flow in the kidneys. An experimental study on ewes also showed that the glomerular filtration rate was significantly ($p < 0.05$) higher in summer (4.2 ± 0.3 mL/min/kg) than in winter (3.0 ± 0.2 mL/min/kg) (Tsuda et al. 1995). Comparatively, the biological pathways between cold spells and deaths from age-related physical debilitation could be rather complicated. The code for age-related physical debilitation is also applicable to frailty, old age, senescence, senile asthenia, and senile disability (WHO 2015). It is a nonspecific diagnosis classified under "general symptoms and signs" that may be used less consistently than more specific causes of death, in part because tests and procedures required to rule out more specific causes of death may not be feasible or practical or may be considered inappropriate or unnecessary. The use of this classification might also be more likely than other mortality outcomes to vary over time or among physicians in different locations or practices (Komiya et al. 2013). However, a reasonable speculation is that, coupled with diminished immune function, a sharp drop in temperature could cause cognitive impairment and physical deterioration in elders (Mäkinen et al. 2006). In 2018, age-related physical debilitation was the third leading cause of death in Japan, killing 109,606 people (E-Stat Portal Site of Official Statistics of Japan). This number may be inevitably rising with the aging of Japanese society. Therefore, our study underscores the fact that more attention and well-designed studies are needed to elucidate this issue.

Our results showed larger effect estimates for all mortality types during longer cold spells and for most mortality types during cold spells that were more intense, which is consistent with previous studies (Chen et al. 2020; Wang et al. 2016). A plausible explanation is that, the lower the temperature or the longer the cold spell, the more work required of the human body to maintain normal temperature. We also found that cold spells earlier in the season were associated with higher risk of death from all causes, overall circulatory disease, cerebrovascular disease, IHD, renal disease, and age-related physical debility, whereas cold spells later in the season were associated with higher respiratory disease and pneumonia mortality. A study of cold spells and all-cause mortality in 99 U.S. cities during the period 1987–2000 reported no difference in associations with more intense or longer cold spells, which were defined using city-specific temperature thresholds and durations of ≥ 2 d, similar to our study (Barnett et al.

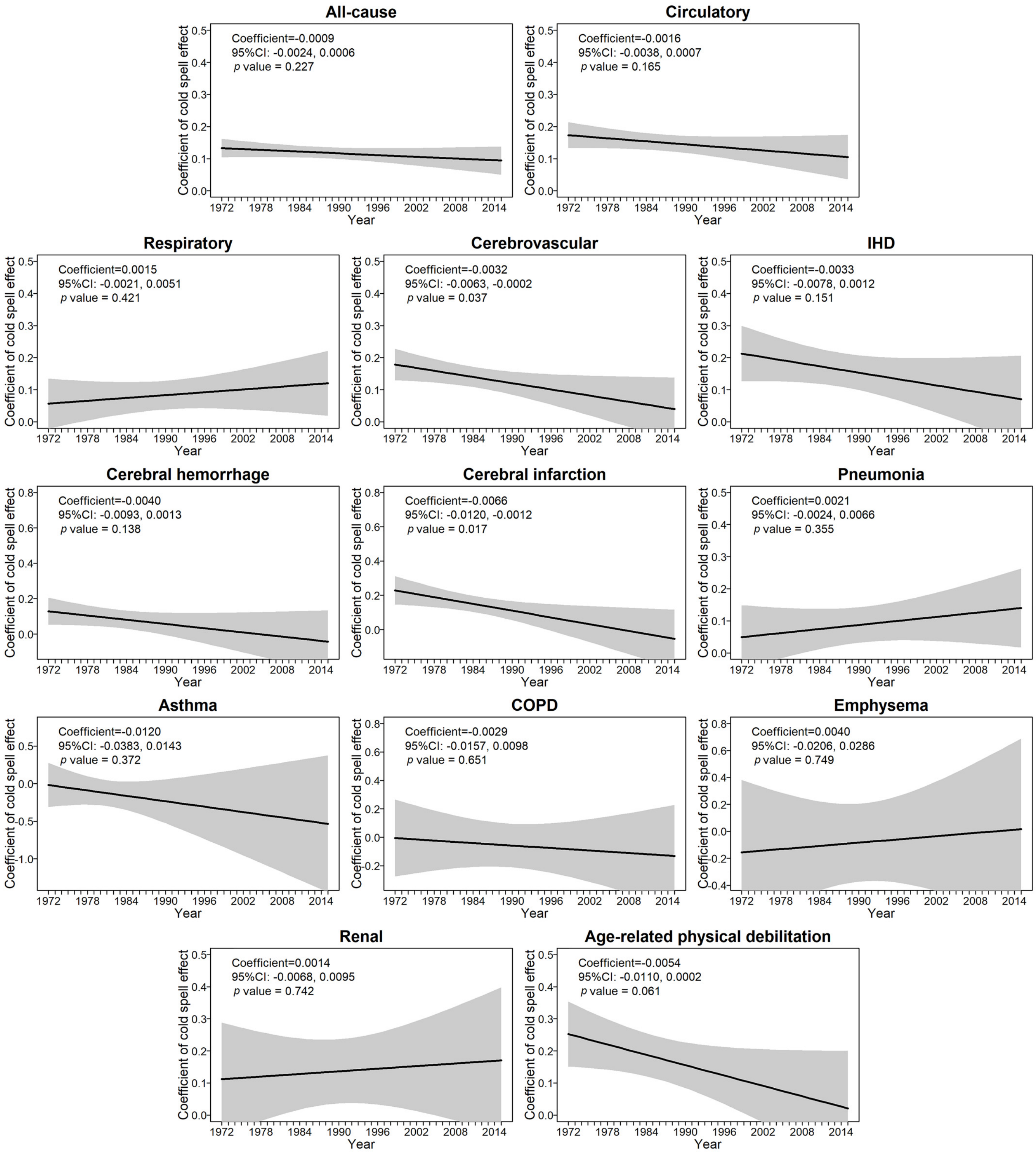

Figure 3. The annual change in coefficient of the association between cold spell and cause-specific mortality in 47 Japanese prefectures during the period 1972–2015. Cold spells were defined as ≥2 consecutive days with daily mean temperatures lower than the prefecture-specific 5th percentile cold season daily mean temperature (for 1972–2015). Prefecture-season-specific cold spell–mortality associations were estimated using quasi-Poisson regression with a distributed lag model, which were then pooled at the national level through random-effect meta-regression models, with "season" as the independent continuous variable (linear) and prefecture-season specific coefficients as the dependent variable. Gray bands are 95% confidence intervals. *p*-values are for the slopes of the annual trends. Note: CI, confidence interval.

2012). Consistent with our finding for all-cause mortality and several specific mortality outcomes, Barnett et al. reported stronger associations between cold spells and mortality for cold spells that occurred earlier in the cold season. The authors suggested this might be explained by the presence of a larger pool of people susceptible to the effects of cold earlier in the cold season, or to a lack of preparedness for colder temperatures (Barnett et al. 2012). However, we found stronger associations of respiratory mortality and pneumonia mortality with cold spells that occurred later in the cold season that warrant further investigation.

Nationally, the strength of cold spell–mortality associations declined from 1972 to 2015 for all causes and most of the more specific outcomes, with significant negative trends ($p < 0.05$) for cerebrovascular disease and cerebral infarction, and a borderline significant decrease ($p = 0.06$) in mortality due to age-related physical debility. However, interpretation is complicated by the potential influence of changes in the application of this nonspecific cause of death over time, which may reflect the change in terminology from "senility" to "age-related physical debility" between ICD-9 and ICD-10, and identification of this temporal trend. A recent global study also showed stable temporal patterns in cold-related mortality in several countries, including Japan, Brazil, Canada, and the United States (Vicedo-Cabrera et al. 2018). The overall nonsignificant declining trends in this nationwide study suggested more complex mechanisms apart from pure adaptation involved in response to cold weather, thus indicating that premature deaths attributed to cold spells could still be a great public health concern in a warming climate. Moreover, the association between cold spell and mortality from overall respiratory disease, pneumonia, emphysema, and renal disease increased at the national level during the period 1972–2015, although it did not reach statistical significance. If so, then the mortality effects of cold spells on populations with these diseases are unlikely to diminish in the near future. In the context of climate change, public health policies and interventions have been almost exclusively designed to minimize health consequences of heat waves (Gasparrini et al. 2015b). Our findings highlight the need to increase the public health resources and allocate them to mitigate cold spell hazards.

Our study of cold spell mortality was national in scale and included assessments of 12 specific mortality outcomes, as well as all-cause mortality, over a 44-y period. In addition, we studied the potential influence of cold spell characteristics (intensity, duration, and seasonal timing), and changes in associations over time. Some limitations of the present study must be acknowledged. First, as with most time-series studies, we used the meteorological data from fixed-site monitoring stations rather than individual direct measurements, which could result in exposure measurement bias. The exposure measurement bias, however, is likely to underestimate the real health effects of cold spells (Lee et al. 2016). Second, although RH was controlled for in the model, it is not a stand-alone humidity variable because it is strongly correlated with temperature (Davis et al. 2016). Third, we did not stratify data analysis by individual characteristics, such as gender, age, and educational attainment due to the lack of relevant data, which may mask vulnerabilities for specific subgroups. However, female, elderly, and individuals with low educational attainment are likely to be the most vulnerable groups (Chen et al. 2019; Chen et al. 2018). Fourth, using a binary exposure approach might lead to the loss of information inherent in the continuous exposure–response between cold temperature and mortality risk. However, the second-level investigation of the role of cold spell intensity in modifying the association accounted for some of the information lost by dichotomizing the exposure. Moreover, this binary approach may be more informative for public health policy and decisions about triggering cold-spell early warning systems.

Conclusions

Understanding the effects of cold spells on human health will increase our ability to address the public health challenges posed by global climate change. In Japan, cold spells were associated with higher mortality from multiple causes of death. With the rapid increase in the aging population of Japan, improvements in clinical and public health practices to reduce the health burden from cold spells are warranted.

Acknowledgments

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